BMP-2/6 heterodimer is more effective than BMP-2 or BMP-6 homodimers as inductor of differentiation of human embryonic stem cells.

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Public Summary:
Bone Morphogenetic Protein (BMP) are secreted proteins in the body that are are involved in differentiation of stem cells into diverse cell types. Therefore, BMPs can be used as main guidance molecules for in vitro differentiation of human stem cells. We have analyzed the ability for inducing differentiation of one such BMPs known as a heterodimer BMP-2/BMP-6 (BMP-2/6) and compared to two other BMPs, namely BMP-2 or BMP-6. We used human embryonic stem (hES) cells H9 as model system for this study. When H9 were incubated in a medium with high concentration of a growth-stimulating protein known as basic fibroblastic growth factor (FGF2), 100 ng/ml of human recombinant BMPs induced morphological changes and differentiation of hES cells in 24 to 48 hours. After 5 days, differentiation markers were detected and quantified by cell biological methods known as quantitative PCR (qPCR) and flow cytometry. BMP-2/6 exhibited stronger activity for the induction of trophectodermal (CDX2) and endodermal (SOX17, GATA4, AFP) markers than BMP-2 or BMP-6 homodimers. BMP-2/6 also induced the expression of cell surface receptors for these BMPs more effectively than BMP-2 or BMP-6 when used at the same concentration and time. Moreover, the percentage of cells expressing the surface endodermal marker of a gene known as CXCR4 was also increased for the BMP-2/6 when compared to both BMP-2 and BMP-6. BMP-2/6 was a more potent activator of cellular signaling than BMP-2 and BMP-6, and the ability to activate these cellular signaling pathways might play a role in its increased potency for inducing hES cell differentiation. Therefore, we conclude that BMP-2/6 is more potent than BMP-2 or BMP-6 for inducing differentiation of hES cells, and it can be used as a more powerful substitute of these BMPs in in vitro differentiation guidance.

Scientific Abstract:
BACKGROUND: Bone Morphogenetic Protein (BMP) signaling pathways are involved in differentiation of stem cells into diverse cell types, and thus BMPs can be used as main guidance molecules for in vitro differentiation of human stem cells.
METHODOLOGY/PRINCIPAL FINDINGS: We have analyzed the ability for inducing differentiation of the heterodimer BMP-2/BMP-6 (BMP-2/6) compared to the homodimers BMP-2 or BMP-6, using human embryonic stem (hES) cells H9 as model system. When incubated in a medium with high concentration of basic fibroblastic growth factor (FGF2), 100 ng/ml of human recombinant BMPs induced morphological changes and differentiation of hES cells in 24 to 48 hours. After 5 days, expression of differentiation markers was induced and quantified by quantitative PCR (qPCR) and flow cytometry. BMP-2/6 exhibited stronger activity for the induction of the expression of trophectodermal (CDX2) and endodermal (SOX17, GATA4, AFP) markers than BMP-2 or BMP-6 homodimers. BMP-2/6 also induced the expression of BMPR2 gene more effectively than BMP-2 or BMP-6 when used at the same concentration and time. Moreover, the percentage of cells expressing the surface endodermal marker CXCR4 was also increased for the heterodimer when compared to both homodimers. BMP-2/6 was a more potent activator of Smad-dependent (SMAD1/5) and Smad-independent signaling (mitogen-activated protein kinases ERK and p38) than BMP-2 and BMP-6, and the activation of these pathways might play a role in its increased potency for inducing hES cell differentiation. CONCLUSIONS/SIGNIFICANCE: Therefore, we conclude that BMP-2/6 is more potent than BMP-2 or BMP-6 for inducing differentiation of hES cells, and it can be used as a more powerful substitute of these BMPs in in vitro differentiation guidance.